

REMARKS

Claims 54 and 57 are pending in this application. No claims have been amended. No additional claims have been cancelled. No new claims have been added.

The Examiner has rejected claims 54 and 57 under 35 U.S.C. § 112, first paragraph, because, in the Examiner's view, the specification does not reasonably provide enablement for the method of treating all diseases enumerated in the claims. Claims 54 and 57 have also been rejected under 35 U.S.C. § 112, first paragraph, it being the Examiner's position that the specification does not reasonably provide enablement for the following: R' and R'' of formula I coming together to form all of the heterocyclic rings claimed, R₁ and R₂ of formulas I and II coming together to form an oxadiazole, and the R' and R'' substituents of R₉ of the compounds of formula II coming together to form heterocycle, the heterocycle being optionally substituted with halogen, cyano, NO₂ or lactone. The Examiner supports both grounds of rejection with a citation to In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Applicants submit that this rejection is not well founded and should be withdrawn as detailed below.

Applicants are not required to specifically teach what is already well known by those skilled in the art. As pointed out in applicants previous response, the specification cites US Patent No. 4,777,167 which describes R' and R'' coming together to form piperidino and pyrrolidino. Other prior art shows, for example, morpholino (Sincar, I. et al., *Journal of Medicinal Chemistry*, 1991, 34, 2248-60); thiomorpholino (US Patent No. 4,618,607); and piperazino (US Patent No. 5,034,395). In view of the specific teachings of the present specification and the general level of skill in the art as exemplified by the above-cited references, a skilled person would readily know how to make compounds wherein R' and R'' of formula I come together to form the heterocyclic rings recited in the claims.

As to the Examiner's second objection, the oxadiazole compounds can be easily prepared by using the appropriate aldehyde (aldehyde 1f of scheme II) and following reaction scheme II. The use of this aldehyde for making dihydropyridines and the

preparation of this oxadiazole-fused benzaldehyde is well documented in the art. See, for example, Leonardi, A., et al., *European Journal of Medicinal Chemistry*, 1998, 33, 399-420; Gasco, A. M., et al., *European Journal of Medicinal Chemistry*, 1996, 31, 3-10; CH 661270. Aldehyde If is also commercially available from MicroChemistry Building Blocks, Order No. mch-bb 2391.

With regard to the Examiner's third objection, applicants once again point out that the claims do not state that the R' and R'' substituents on R₀ of the compounds of Formula II come together to form a ring, as suggested by the Examiner. Accordingly, applicants do not understand the basis of this rejection and request that it be withdrawn.

As to the Examiner's view that the methods of claims 54 and 57 are not enabled, the disclosure fully enables those skilled in the art to practice the claimed methods. The use of dihydropyridine-type calcium channel blockers in treating disorders such as hypersensitivity, allergy, asthma and bronchospasm is well-known in the art, as established by the art already of record in this application. It is further noted that because the compounds administered according to the claimed method of treatment are short acting they exert their effects locally. Thus, these compounds, when administered locally to the lungs, are particularly effective for treating the enumerated disorders. The specification at, for example, page 13, lines 12-24, discloses a number of formulations for local administration of these compounds to the lungs via inhalation, including a solution intended for administration by metered dose inhale, or in a form suitable for a dry powder inhaler or insufflator. Typically, administration via inhalation is accomplished by delivering the specified compounds in the form of an aerosol spray from a pressurized container using a suitable propellant and a valve to deliver a metered dose, as is pointed out in the specification and as is well-known in the art.

The Examiner makes comparisons among several of the disclosed compounds to support the objection that the level of predictability in the art is low, arguing that there is a large variation in nitrendipine binding activity with small changes in structure. Applicants submit that the comparisons drawn by the Examiner among the cited compounds are not correct. Compound 1 is a racemic mixture of compounds that has an IC₅₀ of 0.074 μ M. When the mixture of enantiomers is resolved, which is explained in detail on pages 23-24, Example 1, compounds 2 and 3 are provided. Compound 2 is the

active enantiomer with an IC₅₀ of 0.043 μ M and compound 3 is the less active enantiomer with an IC₅₀ of 0.160 μ M. Compound 6 is also a racemic mixture of compounds. Therefore, it should properly be compared to compound 1, not to the less active enantiomer, compound 3, as the Examiner has done. Thus, the comparisons among compounds drawn by the Examiner do not support the contention that art is highly unpredictable.

Thus, the facts of the present case are similar to those in Wands, wherein the Court found that undue experimentation was not required based on the content of Wands' disclosure. Specifically, Wands provided considerable direction and guidance on how to practice the invention and presented working examples. Further, there was a high level of skill in the art to which Wands' invention pertained and all of the methods needed for practicing the invention were known. In re Wands at 1406.

As in Wands, the present invention relates to an art in which there is a high level of skill. As detailed above, those skilled in the art could easily make compounds commensurate in scope with the claims based on the general knowledge of chemists working in this area and the many exemplified compounds and synthesis routes set forth in the specification. As also discussed above, the use of dihydropyridine-type calcium channel blockers for treating disorders such as hypersensitivity, allergy, asthma and bronchospasm is not highly unpredictable, since the use of these compounds for treating such disorders is well-documented in the art. Taken together, these factors lead to the same conclusion reached by the court in Wands that undue experimentation is not required in order to practice the claimed invention.

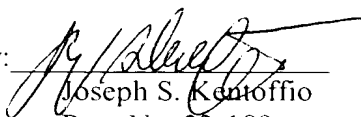
In view of the scope of the disclosure and the level of skill in the art with respect to the use of dihydropyridine-type calcium channel blockers, applicants submit that method of treatment claims 54 and 57 are fully enabled. Accordingly, applicants request that the rejection of claims 54 and 57 under 35 U.S.C. § 112, first paragraph, be withdrawn and that a Notice of Allowance with respect to these claims be issued at the earliest possible date.

Applicants do not believe that any fees are required in connection with the filing of this Response; however, should any fees be necessary please charge Deposit Account No. 10-0750/ORT-1477/JSK.

Serial No. 09/911,050

Should the Examiner have any questions regarding this Response, please contact the undersigned attorney at the telephone number listed.

Respectfully submitted,

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Dated: November 12, 2003